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# Evaluating the Need for Prophylactic Antibiotic Therapy in Infants with Transient Tachypnea of the Newborn: A Triple-Blind Randomized Clinical Trial Study

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***Abstract***

***Background***

Transient tachypnea of the newborn (TTN) is a respiratory disorder caused by delay in the evacuation of the lung fluids. Prophylactic antibiotic therapy is recommended for the risk of sepsis. We aimed to evaluate the effect of the prophylactic antibiotic in infants with TTN.

***Materials and Methods***

This randomized clinical trial study was conducted on all infants, admitted to TTN at Fatemiyeh Hospital, Hamadan, Iran, in 2017. Infants with TTN were randomly stratified into two groups based on whether they received antibiotic or not. Then, the clinical outcomes and laboratory results were examined in the two groups. The categorical data were compared with Chi-square test and the continuous data with t-test using Stata software version 14.0.

***Results***

Out of 100 term and late preterm infants were admitted to TTN. No significant difference was found between two groups in terms of gender (p = 0.228), gestational age (p = 0.728), birth weight (p = 0.974) and other baseline characteristics. Results revealed that no case of sepsis, pneumonia and death were seen in the group received prophylactic antibiotic and the other group did not receive it, but the admission time was lower in infants, who did not receive antibiotic (137.76 ±32.42 versus 159.36± 33.85, p= 0.001).

***Conclusion***

This study showed that antibiotic prescription in TTNs infants without perinatal risk factors has no impact on the disease outcome, and prophylactic antibiotic can be avoided. However, more evidence based on large sample size is required.

***Key Words:*** Antibiotics, Infants, Transient tachypnea of the newborn, Outcome.

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## 1- INTRODUCTION

Transient tachypnea of the newborn is the most common respiratory disorder in term and late preterm infants. It is attributed to delay in evacuation of the lung fluids, leading to respiratory distress (1). In the conducted studies, the incidence of transient tachypnea of the newborn has been reported 5.7 per thousand births (2). In studies conducted in Iran, the incidence of transient tachypnea of the newborn has been reported from 1.6% to 15.7% (3, 4). Risk factors for transient tachypnea of the newborn include cesarean section, male gender, premature birth, macrosomia, multiple pregnancies, prolonged delivery, perinatal asphyxia, fluid overload in mother, especially during the oxytocin prescription, family history of asthma, breech delivery, infant with diabetic mother, the first delivery, and a history of infertility treatment (5).

The clinical symptoms of transient tachypnea of the newborn disease, including respiratory rate higher than 60 breaths per minute and respiratory distress (granting, intercostal muscle retraction, and nasal flaring) usually occur immediately after birth or within the first two hours, and it is usually resolved within 48 to 72 hours, but sometimes complete recovery of the symptoms lasts up to 5 days (6). Although transient tachypnea of the newborn treatment is supportive, infants usually receive antibiotics at least at the first 48 hours after birth until leaving the pneumonia and sepsis diagnosis (5, 7).

The antibiotic treatment is followed with different outcomes in infants with transient tachypnea of the newborn. In a study carried out in Qatar, the admission time was higher in infants with transient tachypnea of the newborn in the group received the antibiotics (8). In a study carried out in United States, infants with transient tachypnea of the newborn, did not receive antibiotic, showed no infectious complications (9). In the study carried out in China, no significant difference was seen between the two groups received antibiotics and did not receive antibiotics in terms of hospital infections including pneumonia, sepsis and necrotizing enterocolitis (10). Based on the limited number of studies conducted, prophylactic antibiotic therapy did not have impact on the disease outcome and even led to prolonged hospitalization. However, the evidence on the antibiotic prescription outcomes in infants with transient tachypnea of the newborn is limited. Given the increasing prevalence of resistance to antibiotics, the prescription of these drugs at the absence of special risk factors of infection should be limited to the necessary cases. The current study was conducted to evaluate the necessity of using prophylaxis antibiotics in infants with transient tachypnea of the newborn admitted to neonatal intensive care unit.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This study was conducted in triple-blind randomized clinical trial method. All infants born in Fatemiyeh Hospital, Hamadan city, Hamadan province of Iran, admitted in the neonatal intensive care unit (NICU) with diagnosis of transient tachypnea of the newborn, were included in the study, if they met inclusion criteria of study. The study lasted for one and a half years from the first day of April of 2016, up to September 2017. The Fatemiyeh Hospital is the largest and main level-3 hospital and a center for high-risk deliveries with mean of 10,000 births per year.

### 2-2. Intervention

Census method was used as sampling method and all infants met the inclusion criteria were investigated in a one and a half year period. Based on the statistics of previous years, the approximate number of patients during this period was estimated

to be about 100 people. Out of these 100 people, 50 were randomly assigned to the intervention group and 50 were assigned to the control group. The patients were randomly assigned to intervention and control groups using block randomization. The infants were unaware of the type of intervention. The physician who examined the patients was not aware of the intervention. The analyzer of the data was unaware of the type of interventions. Just the coordinator of the trial was aware of the intervention. Therefore, the trial will be run as triple blind. Then, those infants met the inclusion criteria were included and they were divided into two intervention and control groups using quadruple random block method. The control group received routine care (such as fluid therapy), and respiratory support as well as ampicillin 25 mg/kg three times per day and amikacin 10 mg / kg twice per day.

The intervention group received only routine cares and respiratory supports. Infants received oxygen at the appropriate concentrations using oxygen and air blender, and Nasal continuous positive airway pressure (NCPAP) started for infants, who needed more than 50% oxygen. This research was conducted in triple-blind form, so that infants were not aware of the type of intervention. Moreover, the physician examining the patients and analyzing the data was not aware of type of intervention. Blood gas samples, complete blood count, C-reactive protein (CRP), blood culture, and chest X-ray were taken from all infants at the first four hours of birth. All infants were examined daily in terms of worsened clinical symptoms (secondary infection) and improvement course.

### 2-3. Ethical considerations

Written consent was taken from the parents of the infants. Before its implementation, the project was approved by the Ethics Committee of Hamadan University of Medical Sciences and was registered at IRCT201609049014N114 at the Iran Clinical Trial Registration Center.

### 2-4. Inclusion and exclusion criteria (5, 6):

Inclusion criteria were as follows: (a) infants with gestational age of 34 weeks and 0 days to 41 weeks and 7 days; (b) diagnosis of transient tachypnea of the newborn defined as respiratory distress with the following conditions; (c) onset within the first 6 hours after birth; (d) lasting for at least 12 hours; (e) chest X-ray findings including at least one of the following: normal or increased pulmonary volumes, ±mild cardiomegaly, increased prominent vascular marking with a sunburst pattern starting from the lung hilum , fluid in interlobar fissures, mild pleural effusion. Exclusion criteria were as follows: (a) having a risk factor for infant sepsis (non-receiving the preventive antibiotics in infants whose mothers have a history of Guillain-Barré syndrome (GBS), diagnosis of Chorioamnionitis, rupture of membrane for more than 18 hours); (b) major congenital anomalies; (c) having Apgar score 7 or lower; (d) history of meconium passage; (e) radiography findings of chest suggestive of pneumonia; (f) symptoms of sepsis; (g) weight less than 2 kg.

### 2-5. Data analysis

After collecting the data, they were entered into the Stata 14.0 software based on the data collection form and analyzed using descriptive statistics, t-test, and Chi-square test. The significance level was considered under 0.05 in this research

## 3- RESULTS

Out of about 14,000 births and 770 infants admitted to the neonatal intensive care unit during one and half year, 100 term and late preterm infants were admitted to transient tachypnea of the newborn. Our research revealed that

67(67%) of the studied infants were male 80(80%) of them were born using cesarean section method. No significant difference was found between two groups in terms of gender (p = 0.228), gestational age (p = 0.728), birth weight (p = 0.974), and other baseline characteristics (**Table.1**). Laboratory findings revealed no significant difference between complete white blood cells count, percentage of neutrophil, and blood culture in the two groups (**Table.2**). In addition, no case of sepsis, pneumonia and death was seen in the group received antibiotic. However, admission time in infants who did not receive antibiotic was significantly lower (137.76 ± 32.42 versus 159.36± 33.85, p= 0.001).

**Table-1**: Baseline characteristics of the study groups

| Variables | Intervention | Control | P-value |
|---|---|---|---|
| | Number (Percent) | Number (Percent) | |
| Gender<br>Boy<br>Girl | 31(62)<br>19(38) | 36(72)<br>14(28) | 0.288 |
| Birth order<br>1<br>2<br>3<br>4<br>5 | 17(34)<br>20(40)<br>8(16)<br>4(8)<br>1(2) | 17(34)<br>20(40)<br>9(18)<br>4(8)<br>0(0) | 0.901 |
| Type of delivery<br>NVD<br>C/S | 11(22)<br>39(78) | 9(18)<br>41(82) | 0.617 |
| Twin<br>Yes<br>No | 0(0)<br>50(50) | 2(4)<br>48(96) | 0.153 |
| Small for Gestational age<br>Yes<br>No | 0(0)<br>50(50) | 3(6)<br>47(94) | 0.079 |
| Gestational diabetes melitus<br>Yes<br>No | 1(2)<br>49(98) | 4(8)<br>46(92) | 0.169 |
| Maternal asthma<br>Yes<br>No | 0(0)<br>50(50) | 1(2)<br>49(98) | 0.315 |
| Gestational age, Mean ± SD (week) | 36.54±1.88 | 36.68±2.13 | 0.728 |
| Birth weight, Mean ± SD (gram) | 2895.7±515.0 | 2899.4±619.8 | 0.974 |
| APGAR Score at 1 Mean ± SD (min) | 7.64± 1.17 | 7.76± 1.09 | 0.598 |
| APGAR Score at 5 Mean ± SD (min) | 9.10±0.73 | 8.90±0.89 | 0.464 |
| Maternal age Mean ± SD (year) | 29.78± 6.58 | 30.14± 5.37 | 0.765 |

SD: standard deviation; NVD: normal vaginal delivery; C/S: cesarean section.

**Table-2**: Laboratory findings at admission

| Variables | Intervention | Control | P-value |
|---|---|---|---|
| | Number (Percent) | Number (Percent) | |
| Positive Blood culture | 0 | 0 | - |
| White blood cells, /mm3 | 14052±4596 | 14012±4217 | 0.963 |
| Segment neutrophil,% | 60.2±11.39 | 58.52±12.85 | 0.490 |

**Table-3**: Effect of prophylactic antibiotic on clinical outcomes

| Variables | Intervention | Control | P-value |
|---|---|---|---|
| | Number (Percent) | Number (Percent) | |
| Pneumonia<br>Yes<br>No | 50(100)<br>0(0) | 50(100)<br>0(0) | - |
| Sepsis<br>Yes<br>No | 50(100)<br>0(0) | 50(100)<br>0(0) | - |
| Death<br>Yes<br>No | 50(100)<br>0(0) | 50(100)<br>0(0) | - |
| Duration of hospitalization<br>Mean ± SD (hour) | 137.76±32.45 | 159.36±33.85 | 0.001 |

## 4- DISCUSSION

Since the clinical symptoms of infants with transient tachypnea of the newborn are not specific, this group of infants receives antibiotics at least 48-72 hours after birth and sometimes 5 days later to leave the pneumonia and sepsis diagnosis (11). This recommendation is not based on the evidence, and unnecessary use of antibiotics, even for a short period, might be harmful for infants, since it might leave negative impact on the natural colonization of gut flora and increase the prevalence of resistance against the antibiotics and nephrotoxic and auto-toxic complications. Thus, prescription of these drugs in the absence of specific risk factors of infection should be limited to the necessary cases (12-15). For this reason, in this research, we did not start the use of antibiotic in the intervention group and examined the infants in terms of clinical symptoms and laboratory results of infant infection in order to minimize potential damage of antibiotics in infants, by observing the accurate diagnostic criteria of the disease and believe in that the need for oxygen and NCPAP alone and in the absence of risk factors of infection are not the reason to start the use of antibiotic (10). No difference was found between two groups in our study in terms of risk factors associated with the disease, including cesarean section, maternal diabetes mellitus and multiple gestation, but 80% of the infants were born with cesarean section, which is less than that found in the study conducted by Dehdashtian et al. (6), with 91.5% and more than that found in the study conducted by Abughalwa et al. (8), with 43.2%. In general, the rate of cesarean section is 40% in Iran (6). As caesarean section is considered as one of the most important risk factors for TTN, and the incidence of transient tachypnea of the newborn has been reported up to 13% in infants born with caesarean section (16), increasing the rate of cesarean section, especially in 3-level hospitals, increases the number of infants with TTN.

Laboratory findings revealed no significant difference between complete white blood cells count, percentage of neutrophil, and blood culture in the two groups. Results of our study are in line with those of other studies (8, 17). No case of positive blood culture was reported in our study and in terms of outcomes of the disease; no case of sepsis, pneumonia and death was seen in both groups. However, in the study conducted by Dehdashtian et al. (6), one case of positive blood culture with coagulase-negative Staphylococcus was seen in the control group and two cases of positive blood culture with the same organism were seen in the intervention

group. In the study carried out by Abughalwa et al. (8), four cases of positive blood culture were seen in the group received the antibiotic (1 case of GBS, 2 staph, 1 case of strep), and 2 cases of positive blood culture with were reported in non-antibiotic group .In the study conducted by Salama et al. (17), two cases of positive blood culture were seen in the non-antibiotic group, and four cases of positive blood culture were seen in the group received antibiotic, but delay in start to use antibiotic did not cause clinical worsening of the patient. Thus, unnecessary antibiotic prescription can be avoided with careful and daily monitoring of the infants in terms of clinical worsening (infection symptoms). Our study also revealed that prophylactic antibiotic therapy did not have an effect on the disease outcome and even led to prolonged hospitalization. In our study, admission time was at least 24 hours lower in neonates, who did not receive antibiotic, which this result is in line with that of other studies (3, 9, 17). Finally, we did not start the use of antibiotic in the intervention group and based on the above studies, prophylactic antibiotic therapy did not have impact on the disease outcome and even led to prolonged hospitalization.

## 5- CONCLUSION

This study is among the few studies, challenging the usefulness of prescribing antibiotics as part of a transient tachypnea of the newborn treatment. It also recommends that unnecessary antibiotic prescription can be avoided with precision in diagnostic criteria of transient tachypnea of the newborn and close monitoring in terms of clinical worsening or blood infection symptoms in infants.

## 6- CONFLICT OF INTEREST: None.

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